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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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HOGAN & HARTSON L.L.P.
500 S. GRAND AVENUE
SUITE 1900
LOS ANGELES, CA 90071-2611

EXAMINER	
NICKOL, GARY B	
ART UNIT	PAPER NUMBER
1642	17

DATE MAILED: 02/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/615,624	BROOKS ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on th cover sheet with the corresp ndence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 26 November 2002 .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-104 is/are pending in the application.

4a) Of the above claim(s) 18-21 and 25-104 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-17 and 22-24 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 6-01-01 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3,6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The Election filed November 26, 2002 (Paper No. 14) in response to the Office Action of August 8, 2002 is acknowledged and has been entered.

Claims 1-104 are pending.

Claims 18-21, and 25-104 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

Claims 1-17, and 22-24 are pending and are currently under consideration.

Applicant's election with traverse of Group I, claims 1-2, 4-5, 7-17, 22-24 in Paper No 14 is acknowledged. The traversal is on the ground(s) that the inventions have not been shown to be independent and the examination of all groups would not impose a serious burden on the examiner. This is not found persuasive. MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Here, the inventions of the various groups are distinct for the reasons set forth in Paper No. 12.

As to the question of burden of search, the inventions are classified differently, necessitating different searches in the literature. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group.

Applicants further request that at least claims 1-24 (Groups I-VI) be examined together. This argument has been considered and is found persuasive, in-part. Groups I and II (Claims 1-17, and 22-24) are re-joined.

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Drawings

Color photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) is granted permitting their use as acceptable drawings. In the event that applicant wishes to use the drawings currently on file as acceptable drawings, a petition must be filed for acceptance of the color photographs or color drawings as acceptable drawings. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and an amendment to the first paragraph of the brief description of the drawings section of the specification which states:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the U.S. Patent and Trademark Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to AND claims **15-16** are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

The claims are drawn to monoclonal antibody **FM155.**

It is unclear if a cell line which produces an antibody having the exact structural and chemical identity of monoclonal antibodies selected from the group consisting of **FM155,** are known and publicly available, or can be reproducibly isolated without undue experimentation. Clearly, without access to the hybridoma cell lines producing said monoclonal antibodies, it would not be possible to practice the claimed invention. Therefore, suitable deposits for patent purposes are required. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

Furthermore, any future amendment to the specification that discloses cells which produce said monoclonal antibodies (i.e. specifically deposited hybridomas) must make sure that that all of the conditions of 37 CFR sections 1.801 through 1.809 have been met. If the deposits

were made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicants, assignees or a statement by an attorney of record over his or her signature and registration number stating that the deposits have been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository **is required**. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves these specific matters to the discretion of each State. Additionally, amendment of the specification to recite the date of the deposit and the complete name and address of the depository is required.

In view of the above, it would require undue experimentation to reproduce the claimed antibodies of FM155. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 8-14, 17, 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by MELVIN *et al.* (WO 97/00449, January 1997).

The claims are drawn to an antagonist that inhibits angiogenesis by modifying protein-protein interactions, wherein the protein-protein interactions comprise interactions between at least one amino acid sequence within a first protein and at least one amino acid sequence within a second protein (Claim 1); wherein the first protein is MMP-9 (Claim 2); wherein the protein–protein interactions cause co-localization of the first protein and the second protein on a cell surface or a blood vessel (Claim 8); wherein said antagonist inhibits angiogenesis, or tumor growth, or metastasis, or a disease state wherein said disease is psoriasis, macular degeneration, a neurological disease, or restenosis in a tissue (Claims 9-13); wherein said antagonist is a monoclonal antibody or a polyclonal antibody (Claims 14, 17); wherein the antagonist is a humanized or chemically modified monoclonal antibody, a fragment of a monoclonal antibody, or wherein the antagonist is conjugated to cytotoxic or cytostatic agents (Claims 22-24).

Melvin *et al.* teach therapeutic antagonists of matrix metalloproteinase-9 (MMP-9) in the form of polyclonal and monoclonal antibodies (page 4, lines 1-30) wherein such antagonists would modify the protein-protein interactions of MMP-9 because MMP-9 interacts with at least one amino acid sequence within a second protein as substrates for MMP-9 include other proteins such as the protein components of the extracellular matrix. Although the prior art does not specifically teach that the protein-protein interactions cause co-localization of the first protein and the second protein on a cell surface or a blood vessel, such natural biological consequences do not lend patentable weight to the claimed invention, a product; and are thus not considered to have patentable weight for the purposes of comparing the claimed invention with the prior art. Melvin *et al.* further teach that these therapeutic antagonists can be used to inhibit a disease state such as cancer and that the antagonists can be a humanized or chemically modified monoclonal

antibody, a fragment of a monoclonal antibody, or wherein the antagonist is conjugated to cytotoxic or cytostatic agents (page 6, lines 25+, and page 16). Although the reference does not specifically teach that the antagonists inhibit angiogenesis, metastasis, psoriasis, macular degeneration, a neurological disease, or restenosis, the claims are drawn to the product *per se* and inherently, such therapeutic antagonists would function the same as to that which is claimed. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claims 1, 3, 6, and 8-13 are rejected under 35 U.S.C. 102(b) as being anticipated by RUOSLAHTI *et al.* (WO 95/14714, 1995, IDS).

The claims are drawn to an antagonist that inhibits angiogenesis by modifying protein-protein interactions, wherein the protein-protein interactions comprise interactions between at least one amino acid sequence within a first protein and at least one amino acid sequence within a second protein (Claim 1); wherein the first protein is a β1 containing integrin wherein said integrin is α5β1 integrin (Claims 3,6); wherein the protein–protein interactions cause co-localization of the first protein and the second protein on a cell surface or a blood vessel (Claim 8); wherein said antagonist inhibits angiogenesis, or tumor growth, or metastasis, or a disease

state wherein said disease is psoriasis, macular degeneration, a neurological disease, or restenosis in a tissue (Claims 9-13).

Ruoslahti *et al.* teach therapeutic antagonists of $\alpha5\beta1$ integrins wherin such antagonists would modify the protein-protein interactions of $\alpha5\beta1$ integrin because $\alpha5\beta1$ integrin interacts with at least one amino acid sequence within a second protein such as fibronectin, an ECM ligand (page 2, line 3). Ruoslahti further teach that such antagonists are useful for inhibiting metastasis of tumor cells (page 4, line 28). Although the prior art does not specifically teach that the protein-protein interactions cause co-localization of the first protein and the second protein on a cell surface or a blood vessel, such natural biological consequences do not lend patentable weight to the claimed invention, a product; and are thus not considered to have patentable weight for the purposes of comparing the claimed invention with the prior art. Although the reference does not specifically teach that the antagonists inhibit angiogenesis, psoriasis, macular degeneration, a neurological disease, or restenosis, the claims are drawn to the product *per se* and inherently, such antagonists would function the same as to that which is claimed. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claims 1, 3, 6, 8-14, 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Newton *et al.* (Int'l. Jnl. Oncol., Vol. 6, pages 1063-1070, 1995).

Newton *et al.* teach therapeutic antagonists of $\alpha5\beta1$ integrins including monoclonal and polyclonal (page 1068, 1st column, 2nd paragraph) antibodies wherein such antagonists would modify the protein-protein interactions of $\alpha5\beta1$ integrin because $\alpha5\beta1$ integrin interacts with at least one amino acid sequence within a second protein such as fibronectin, an ECM ligand (page 2, line 3). Newton *et al.* further teach that such antagonists are useful for inhibiting metastasis of tumor cells (abstract). Although the prior art does not specifically teach that the protein-protein interactions cause co-localization of the first protein and the second protein on a cell surface or a blood vessel, such natural biological consequences do not lend patentable weight to the claimed invention, a product; and are thus not considered to have patentable weight for the purposes of comparing the claimed invention with the prior art. Although the reference does not specifically teach that the antagonists inhibit angiogenesis, psoriasis, macular degeneration, a neurological disease, or restenosis, the claims are drawn to the product *per se* and inherently, such antagonists would function the same as to that which is claimed. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-14, 17, 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over MELVIN *et al.* (WO 97/00449, January 1997) in combination with the teachings of Newton *et al.* (Int'l. Jnl. Oncol., Vol. 6, pages 1063-1070, 1995).

Melvin *et al.* teach as set forth above.

Melvin *et al.* do not teach an antagonist that inhibits angiogenesis by modifying protein-protein interactions, wherein the protein-protein interactions comprise interactions between at least one amino acid within MMP-9 **and at least one amino acid sequence within α5β1 integrin**.

Newton *et al.* teach as set forth above which includes the successful inhibition of human breast carcinoma cell metastasis in mice by administration of an antagonist to at least one amino

acid sequence within the α5β1 integrin (abstract, page 1067, 2nd column) wherein said antagonist includes monoclonal and polyclonal (page 1068, 1st column, 2nd paragraph) antibodies.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the antagonist of Melvin *et al.* (anti-MMP-9 antibodies) with the antagonist of Newton *et al.* for the purposes of inhibiting tumor metastasis and angiogenesis and one would have been motivated to do so because one would have a reasonable expectation that that the combination of the two antagonists to form a new therapeutic antagonist would achieve a greater effect than either antagonist alone based on the successful teachings of Newton *et al.* Although the prior art does not characterize that the protein-protein interactions "cause MMP-9 to bind the β1-containing integrin", the claims are drawn to the product *per se* and such natural biological consequences do not lend patentable weight.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
February 10, 2003